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Excretion of iodinated contrast media in human breast milk: surprising results

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To-the-Editor

Although the ESUR- and ACR-guidelines on contrast media recommend continuing breast-feeding following the application of an iodinated contrast medium (ICM) [1, 2], in clinical routine it is questionable what to advise a lactating woman. Therefore, we analysed the literature dealing with this subject, and present herein the surprising result.

We found eight publications dealing with ICM concentrations in breast milk (table 1) [3-10]. The most recent publication is 25 years old, and the others are much older (mean 39.9 years, range 25 – 64 years). The papers present breast-milk analyses following the application of seven different ICM compounds, three of them are non-ionic (iohexol, iobitridol,

and metrizamide). Most of the analysed ICMs (metrizoate, iodamide, metrizamide, and iopanoic acid) have been discontinued (table 1).

The total number of patients investigated in six papers [5-10] was only twenty-two. Following the subtraction of patients receiving compounds that are no longer on the market, a group of seven patients remains (four received iohexol, and three amidotrizoate) as basis for the guidelines [1, 2].

The methods used to detect ICM in human breast milk range from titration with sodium thiosulphate, to spectrophotometry, UV-spectrometry, Technicon Analyzer and high pressure liquid chromatography (HPLC) (table 1). While older papers detected iodine [6, 7, 9, 10], others directly determined the ICM-molecules and their concentration in the human milk [5, 8].

The obtained results (peak values as well as iodine concentrations) vary in wide ranges (table 1). Peak values of iodine/ICM excreted in breast milk were measured at 0.75h up to 60h following ICM-application (table 1). Since most of the authors did not perform continuous detections in human breast milk, the real peaks are unknown, so far. The same is true for the iodine- / ICM-concentration in breast milk. Only Ilett et al. [8] analysed the total milk volume excreted in 24h. The other authors measured the iodine- /ICM-concentration in a few distinct samples following ICM-application for contrast-enhanced image-guided procedures [5, 9, 10]. Consequently, we interpolated the missing values, and calculated the iodine content in 24h human breast milk (table 1). Thereby, the amounts of detected iodine in breast milk range from 0 mg/24h to 36.5 mg/24h. Possible reasons for these different results may be that the investigated patient group was too small, the use of different analytical methods, and different sampling times following ICM-application [3-10].

Obviously, lactating women seem to belong to different excretion types, namely low, medium and high [5, 9]. Studies in greater patient groups are warranted to confirm this assumption, and to present reliable data of ICM-concentrations in human breast milk. Currently, we do not know much about ICM-concentrations in human breast milk. The frequent repeated

statement “less than 1% of the ICM-dose applied to the mother is excreted with the breast milk”, could be correct or another myth [11].

Interestingly, the two papers, which report studies in animals [3, 4] have been cited as often as the six papers focussing on human analyses [5-10] (108 vs. 112) (table 1). Citation has a potentiating effect. The more the papers are cited the greater the impression that the mentioned data are reliable. Surprisingly, none of the 220 papers citing the sparse literature on iodine- / ICM- concentrations in breast milk presented a synopsis as we are in this paper, and no author hazarded the opinion that the analysed cohort is much too small for recommendations or guidelines. This is indeed surprising, because with respect to other papers focussing on ICM-hypersensitivity reactions, for example, the greater the number of patients studied the better [12, 13].

Taken together, a detailed search for papers presenting data of ICM concentrations in breast milk following ICM-injection leads to the detection of eight publications (75% of papers deal with results in humans). Results of twenty-two breast feeding women receiving six different ICMs (two non-ionic, and four ionic), are described, so far. Currently, only two of these ICMs are EMA- or FDA-approved, and on the market (table 1). Therefore, the problems with these six human papers are; the number of analysed breast-feeding women is too small, the methods used for detecting contrast media or iodine are heterogenous, and only one non-ionic ICM (namely iohexol) has been analysed. The published studies differ widely in the range of ICM concentrations reported (factor 100: 0.3 up to 36.5 mg iodine per day). This means, the existing data are not a suitable basis on which to base guidelines. In other words, now the only recommendation is to stop breast-feeding for 24 hours following the injection of an iodinated CM.

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References

1. European Society of Urogenital Radiology, ESUR Guidelines on Contrast agents. Version 10.0. http://www.esur.org/esur-guidelines/ Accessed March, 2018.

2. ACR Committee on Drugs and Contrast Media. ACR manual on contrast media, version 10.3. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed March 15, 2019.

3. Bourrinet P, Dencausse A, Havard P, Violas X, Bonnemain B. Transplacental passage and milk excretion of iobitridol. Invest Radiol 1995;30:156–158.

4. Mützel W, Speck U. Pharmacokinetics and biotransformation of iohexol in the rat and the dog. Acta Radiol Suppl 1980;362:87–92.

5. Nielsen ST, Matheson I, Rasmussen JN, Skinnemoen K, Andrew E, Hafsahl G. Excretion of iohexol and metrizoate in human breast milk. Acta Radiol 1987;28(5):523–526.

6. Texier F, Roque D'Orbcastel O, Etling N. Stable iodine level in human milk after pulmonary angiography. Presse Med 1983;19:769.

7. FritzJohn TP, Williams DG, Laker MF, Owen JP. Intravenous urography during lactation. Br J Radiol 1982;55:603–605.

8. Ilett KF, Hackett LP, Paterson JW, McCormick CC. Excretion of metrizamide in milk. Br J Radiol 1981;54:537–538.

9. Weyrauch U, Volkhardt V, Speck U. Transfer of Amidotrizoate in Maternal Milk Following Phlebography in a Patient 10 Days Post Partum. Röfo Fortschr Geb Rontgenstr Nuklearmed 1977;127:275-6.

10. Holmdahl KH. Cholecystography during lactation. Acta Radiol 1956;45:305–307.

11. Böhm I, Morelli J, Nairz K, Silva Hasembank Keller P, Heverhagen JT. Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review. Postgrad Med 2017;129(2):259-266.

12. Schild HH, Kuhl CK, Hübner-Steiner U, Böhm I, Speck U. Adverse Events After Unenhanced and Monomeric and Dimeric Contrast-Enhanced CT: A Prospective Randomized Controlled Trial. Radiology 2006;240:56-64.

13. Park HJ, Son JH, Kim TB, Kang MK, Han K, Kim EH, Kim AY, Park SH. Relationship between Lower Dose and Injection Speed of Iodinated Contrast Material for CT and Acute Hypersensitivity Reactions: An Observational Study. Radiology. 2019;293(3):565-572.

Table 1 – Overview of results published in eight papers. * According to google scholar; ** including Switzerland; *** paper online not available; **** interpolated and calculated.

first author, year	pats	animals	contrast agent	times cited*	method	approved and on the market in EU**/USA	peak of iodine/ICM excretion in the milk	mg iodine in 24h breast milk
Bourrinet P 1995	---	2 goats	Iohexol	27	UV-spectrometry	yes / yes	8h and 60h	n.d.
Bourrinet P 1995	---	3 goats	Iobitridol	"	UV-spectrometry	yes / no	4h	n.d.
Nielsen ST 1987	4	---	Iohexol	45	HPLC	yes / yes	3h, 6h, 3h, 0.75h	6.2; 7.1; 8.1; 36.5****
Nielsen ST 1987	2	---	Metrizoate	"	"	no / no	6h, 1.5h	3.84; 5.0****
Texier F 1983	1	---	Amidotrizoate (diatrizoate)	4	Technicon Analyser	yes / yes	within 24h	31
FritzJohn TP 1982	1	---	Iodamide	23	spectrophotometry	no / no	---	0
FritzJohn TP 1982	1	---	Amidotrizoate (diatrizoate)	"	"	yes / yes	---	0
Ilett KF 1981	1	---	Metrizamide	23	HPLC	no / no	unknown	0.3
Mützel W*** 1980	---	rats, dogs	Iohexol	81	unknown	yes / yes	unknown	unknown
Weyrauch U 1977	1	---	Amidotrizoate (diatrizoate)	0	Technicon Analyser	yes / yes	7h	9.8****
Holmdahl KH 1956	5	---	Iopanoic acid (Telepaque®)	17	incineration, oxidation, and titration with sodium thiosulphate	no / no	17h, 11h, 11h, 19h, 19h	29.9; 17.1; 29.23; 6.72; 21.04
Holmdahl KH 1956	6	---	Iopanoic acid (Bilijodon®)	"	"	no / no	15h, 15h, 15h, 11h, 23h, 19h	9.74; 10.5; 9.19; 25.64; 10,14; 16.60